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A hospital-based observational comparative study of efficacy of intracameral voriconazole and oral ketoconazole in deep keratomycosis

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ABSTRACT

BACKGROUND: Fungal keratitis, one of the most common causes of ocular mycosis, is the second most common cause of blindness in the world, after cataracts. The aim of the study was to compare the efficacy of conventional topical, systemic medications and intracameral voriconazole injection in visual and structural outcomes in keratomycosis.
MATERIAL AND METHODS: We conducted a hospital-based observational study of 45 patients of 45 eyes with smear-positive fungal keratitis. Patients were categorized into three groups: Group I received systemic topical with oral ketoconazole 200 mg, Group II — topical medications with intracameral voriconazole 50 µgm/0.1 mL, Group III — topical medications with both oral ketoconazole 200 mg and intracameral voriconazole 50 µgm/0.1 mL.
RESULTS: The common fungal organism is identified as *Fusarium*. The mean final visual acuity (VA) was 1.25 ± 0.32, 1.47 ± 1.05, and 1.22 ± 0.37 logMAR in Group I, group II, and Group III, respectively. The mean improvement in VA was 0.33 ± 0.07, 0.01 ± 0.71, and –0.19 ± 0.02 logMAR without significant change ($p = 0.9$). There was a significant difference in VA between the final postoperative follow-up period and baseline in Group I cases ($p = 0.0019$). Whereas no difference in VA between the final postoperative follow-up period and baseline in either Group II ($p = 0.0671$) or Group III ($p = 0.1505$) cases. The difference in time between the disappearance of hypopyon and the mean time to infection healing was not statistically significant ($p = 0.1$). Three cases in each group were perforated, and keratoplasty was performed. These perforated cases did not show culture positive. Histopathology identified the isolated organisms as *Aspergillus* species (n = 3) and *Fusarium* species (n = 2) in the corneal buttons.
CONCLUSION: The differences in VA between the three methods were not statistically significant, indicating no treatment method superior to others (inter-group). However, in Group I, there was a significant difference in VA between the final postoperative follow-up period and baseline ($p = 0.0019$). There was no difference in VA between these time intervals in either Group II ($p = 0.0671$) or Group III ($p = 0.1505$). Within-group or intra-group analysis reveals that the Group I method is more effective for VA. The success rate of the method depended cumulatively on the duration of intracameral voriconazole in the anterior chamber, non-drainage of hypopyon, and individual clinical response.

KEY WORDS: keratomycosis; *Aspergillus*; voriconazole; hypopyon

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INTRODUCTION

Globally, microbial keratitis is the major cause of blindness [1]. It is common in developing countries, and both active/resolved infectious keratitis are significant indications for corneal transplantation [2]. One-third of corneal ulcers are due to fungal etiology in India [3]. Infection caused by fungal keratitis (FK) is more virulent/damaging than bacterial origin. Fungal keratitis more likely perforates the cornea than bacterial keratitis (OR = 5.86, 95% CI: 2.06–16.69) [4, 5]. Ocular trauma is a predisposing factor for FK reported from developing countries [3, 4, 6].

If microorganisms enter deeper into the corneal stroma by Descemet's membrane/anterior chamber/sclera, eradication is most difficult. The invasion subsequently leads to tissue damage which can further disrupt the visual axis. Hence, early diagnosis of FK is imperative to prevent visual complications [7].

Ketoconazole, an oral imidazole antifungal agent, is effective in treating mucocutaneous fungal infections, both superficial and deep fungal infections. It is metabolized in the liver and excreted as an inactive drug in bile and, to a small extent, urine. The initial half-life of ketoconazole is 2 hours, whereas, with a β-phase, its half-life is 9 hours after 8–12 hours ingestion. Ketoconazole inhibits the glucuronidation of UGT2B7 substrates zidovudine and lorazepam. It requires acidic pH for systemic absorption. Ketoconazole exhibits low apparent oral bioavailability, resulting in low serum concentrations when administered with cimetidine or antacids. Neutropenic patients poorly absorb ketoconazole, which may account for prophylactic failure [8].

Voriconazole is the first available second-generation triazole, a broad-spectrum antifungal agent. It inhibits the cytochrome P450 14-α-demethylase (P450 14DM), which causes disrupting the close packing of the acyl chains of phospholipids, thereby reducing fungal growth. Voriconazole is rapidly absorbed within 2 hours after oral administration [9, 10].

The purpose of this study was to compare the efficacy of conventional topical, systemic medications and intracameral voriconazole injection in visual and structural outcomes in keratomycosis.

MATERIAL AND METHODS

The study protocol was approved by Institutional Ethics Committee, Sankar Foundation Eye Institute, Visakhapatnam, India. There was no new intervention/protocol/drug used in this study. Informed consent was obtained from each patient. We collected the data retrospectively from our electronic medical records.

A randomized control study was conducted on 45 patients with smear-positive FK reporting to the Cornea Department in Tertiary Eye Care Center in Visakhapatnam, India, from August 2016 to January 2018.

The inclusion criteria were: patients who had involvement of more than anterior one-third of the cornea with concomitant hypopyon, and patients with corneal scraping positive for fungal filaments in direct smear examination by one or more of the methods used.

Exclusion criteria were: one-eyed patients, children < 15 years of age, cases with keratitis limited to the anterior third of the stroma, perforated corneal ulcers or those with impending perforation, involvement of the adjacent sclera, ulcers with clinical features of noninfective and autoimmune conditions, fungal ulcer associated with endophthalmitis, presence of dacryocystitis, presence of other comorbidities such as corneal anesthesia, exposure or dry eye and patients who received/required immunosuppressants, HIV-positive or diabetic, or those who had a bilateral infection.

All patients underwent routine ophthalmic examination. The history of presenting complaints, trauma, treatment received, etc., were recorded. Slit-lamp microscopy was performed to analyze the corneal ulcer size, depth of infiltrates, endothelial plaque, satellite lesions, hypopyon size, nature of hypopyon, and identification of cataracts. Syringing was done to find chronic dacryocystitis. Posterior segment evaluation was performed using 90D biomicroscopy and, if required, B-scan ultrasonography. Systemic examination was done to detect hypertension, diabetes, and immunocompromised status. Scraping of the corneal ulcer was done for microbiological investigations. The diagnosis of the fungal corneal ulcer was made based on history, clinical features, and microbiological investigations, including Gram-staining. Sabouraud dextrose agar (SDA) was used for fungal culture.

All study subjects were randomly divided into three treatment groups:

- Group I (n = 15) received topical medications + oral ketoconazole 200 mg twice daily;
- Group II (n = 15) received topical medications + intracameral voriconazole 50 µgm/0.1 mL;

- Group III (n = 15) received topical medications + oral ketoconazole 200 mg twice daily + intracameral voriconazole 50 µgm/0.1 mL.

Topical medications included natamycin 5% and voriconazole 1% hourly, cycloplegic homatropine 2% thrice daily, and intraocular pressure (IOP) lowering drugs were used if required.

The duration of oral KCZ treatment was 21 days. There was no change in liver and renal function test and no side effects in any systemic function recorded.

Intracameral voriconazole was injected under the operating microscope after the instillation of topical proparacaine. A volume of 50 µg voriconazole in 0.1 mL was injected into the anterior chamber using a 30-gauge needle attached to a 1.0-mL regular insulin syringe.

In follow-up, various parameters were examined, including visual acuity (VA), size and depth of ulcer, size of hypopyon, and other ocular and clinical variables.

Treatment success was defined as the resolution of stromal infiltrates, endothelial plaque's disappearance, and hypopyon's disappearance. Treatment failure was defined as an increase in epithelial defects, stromal infiltrate and hypopyon, an increase in corneal thinning, and impending perforation.

After 72 h, repeat intracameral voriconazole injection was done in Groups II and III. The time interval between the two injections was 72 h, and the maximum number of three injections was given. If there was any further ulcer perforation, the case was subjected to therapeutic PK.

Statistical analysis

Quantitative data were represented as mean and standard deviation (SD). Data were analyzed using SPSS software version 22. The one-way analysis of variance (ANOVA) test was adopted to compare the VA, best-corrected visual acuity (BCVA), ulcer size, hypopyon size, fungal spectrum, and follow-up measurements. Student's t-test analysis was done to compare the VA between baseline and final follow-up period.Ap-value of less than 0.05 was considered statistically significant.

RESULTS

All patients were randomly divided into three groups, with each group of 15 patients. There were 7 patients in Group I, 5 patients in Group II, and 3 patients in Group III with vegetative trauma. There were no statistically significant differences in age (p = 0.5), initial ulcer size (p = 0.5), and VA at baseline (p = 0.4) in the studied groups (Tab. 1).

Upon potassium hydroxide (KOH) smear, all samples showed filamentous fungi. The most common fungal isolate was *Fusarium* (Tab. 2). No cases had cultures positive for the bacterial organism. There was no significant difference in the treatment success rate in all three groups (p = 0.7). The difference in mean time to the disappearance of hypopyon (p = 0.09) and mean time of infection healing did not show significant difference (p = 0.1) (Tab. 3). The mean final VA difference in the three groups was not statistically significant (p = 0.9) (Tab. 3).

Visual acuity did not differ statistically between the final postoperative follow-up period and baseline in either Group II (p = 0.0671) or Group III (p = 0.1505). In Group I, there was a significant difference in VA between the final postoperative follow-up period and baseline, with a p-value of 0.0019 (Tab. 4).

Table 1. Demographics and baseline measurements

	Group I [T + S]	Group II [T + IC]	Group III [T + S + IC]	p-value
Number	15	15	15	–
Male	9	9	7	> 0.05
Female	6	6	8	> 0.05
Age (mean + SD)	50.6 ± 9.75	55.73 ± 10.77	50.0 ± 11.19	0.5
Vegetative trauma	7	5	3	
Initial VA (logMAR) (mean ± SD)	1.58 ± 0.25	1.46 ± 0.34	1.41 ± 0.35	0.4
Ulcer size [mm^2] (mean ± SD)	16.56 ± 4.82	18.86 ± 6.66	17.48 ± 4.29	0.5
Hypopyon size [mm] (mean ± SD)	2.23 ± 0.82	2.33 ± 1.23	2.4 ± 1.00	0.9

*One-way analysis of variance (ANOVA); T — topical medications; S — oral ketoconazole; IC — intracameral voriconazole; SD — standard deviation; VA — visual aquity

Table 2. Distribution of fungal organisms in all groups

Organism	Group I [T + S]	Group II [T + IC]	Group III [T + S + IC]
Aspergillus	5	6	4
Fusarium	6	6	6
Dematiaceous	1	0	1
No growth	3	3	4

*One-way Analysis of variance (ANOVA); T — topical medications; S — oral ketoconazole; IC — intracameral voriconazole

Table 3. Follow-up measurements in all groups and their association

Outcome	Group I [T + S]	Group II [T + IC]	Group III [T + S + IC]	p-value
Treatment success (n, %)	11	12	10	0.7
Time to disappearance of hypopyon [days] (mean ± SD)	22.26 ± 10.9	29.6 ± 9.21	29.4 ± 10.6	0.09
Time to healing [days] (mean ± SD)	32.86 ± 13.38	40.46 ± 10.35	40.73 ± 13.10	0.1
Time to healing [days] (range)	10–55	21 - 70	25–67	
Final BCVA (logMAR) (mean ± SD)	1.21 ± 0.35	1.22 ± 0.35	1.21 ± 0.39	0.9

*One-way Analysis of variance (ANOVA); T — topical medications; S — oral ketoconazole; IC — intracameral voriconazole; SD — standard deviation; BCVA — best-corrected visual acuity

Table 4. The mean difference in visual acuity between each group before and after treatment

Outcome measure	Baseline interval	Final VA	Mean difference	t-statistic	p-value
Group I [T + S]	1.58 ± 0.25	1.21 ± 0.35	0.380	3.422	0.0019*
Group II [T + IC]	1.46 ± 0.34	1.22 ± 0.35	0.240	1.905	0.067 (NS)
Group III [T + S + IC]	1.41 ± 0.35	1.21 ± 0.39	0.200	1.478	0.15 (NS)

*t -stat; The difference between the observed means in two independent samples is computed using this procedure. The difference is reported with a significance value (p-value) and a 95% confidence interval (CI). The p-value represents the likelihood of obtaining the observed difference between the samples if the null hypothesis is true. ns stands for not significant; T — topical medications; S — oral ketoconazole; IC — intracameral voriconazole; VA — visual acuity; NS — non significant

Three cases in each group underwent therapeutic keratoplasty. All these cases did not show any culture positive. Histopathology results identified *Aspergillus* (n = 3) and *Fusarium* (n = 2) in corneal buttons.

DISCUSSION

Unlike bacteria, fungi can penetrate into the Descemet's membrane and enter the anterior chamber, resulting in hypopyon. Topical antifungals were not very effective in mycotic keratitis cases due to poor penetration. Antifungal drugs and drug instillation procedures are being explored to avoid problems raised by other treatments.

Kaushik et al. [12] evaluated the use of intracameral drugs in mycotic keratitis. Intracameral amphotericin B is associated with side effects such as anterior chamber inflammation, pain, and cataract formation. Hence intracameral voriconazole without these side effects shows a better antifungal spectrum, we administered intracameral voriconazole 50 µg instead of amphotericin B.

In the present study, patients with clinical features of mycotic keratitis and diagnosed with KOH preparation positive were enrolled. Prakash et al. achieved success in three cases by repeated intra-stromal injection of voriconazole, and Shen et al. reported successful resolution of the anterior chamber by repeated intracameral voriconazole [12, 13]. In our study, we used intracameral voriconazole injection in Groups II and III as a loading dose and repeated up to three injections if needed. Since voriconazole remains in the anterior chamber up to 22 minutes after injection, it is difficult to evaluate its significant role in resolution. In other studies, the reported aqueous voriconazole concentration measured after topical instillation ranged from 1.9 mg/mL in non-inflamed eyes to 3.2 mg/mL in inflamed eyes, more than minimum

inhibitory concentration (MIC) for *Aspergillus* and *Candida* keratitis [14, 15]. Study shows that frequent topical voriconazole instillation would have a greater impact on infection resolution than intracameral injections.1% voriconazole eye drops were well tolerated in the study patients. In our study, patients did not have severe inflammation and pain after intracameral injection in contrast to observations by Vikas et al. [16]. Unlike intracameral amphotericin B, which causes inflammation and pain [17].The current study did not reduce the frequency of instillation after the initial better response. We have also used systemic ketoconazole in Groups I and III, which would have hastened the healing though there was no statistically significant difference in treatment success. Systemic voriconazole was not used in our study. The success rate in intracameral injections of voriconazole was less significant in the current study than in the survey by Vikas et al.

In this study, the mean ulcer size was 18.86 and 17.48 mm^2 in the intracameral voriconazole groups and 16.56 mm^2 in the topical treatment group. The mean ulcer size was smaller than observed by Sharma et al. The mean hypopyon size was more significant (2.23, 2.33, 2.40 mm in Groups I, II, and III, respectively) than observed in the study by Sharma et al. [18].

In our study, the mean time of healing was 32.86 ± 13.38 days (range, 10–55 days) after treatment with topical and systemic antifungal agents, 40.4 ± 10.35 days (range, 21–70 days) in patients treated with topical and intracameral voriconazole and 40.73 ± 13.1 days (range, 25–67 days) in patients treated with all modes of treatment. The mean time to heal was shorter in Group I than in other groups, indicating that intracameral voriconazole had no benefits in disease resolution. However, the difference did not attain significance (p = 0.1).

Many cases of mycotic keratitis have associated hypopyon. Various studies [17–20] have shown that concomitant drainage of hypopyon in patients with minimal hypopyon may improve the outcome because it causes debulking of the infective load. In our study we did not drain hypopyon, which is a drawback and could be the reason for delayed healing. There was no case of any exacerbation in inflammation or increase in hypopyon post-intervention in Groups II or III. However, the time taken for hypopyon disappearance was longer in Group III than in other groups.

CONCLUSION

The current study does not show a significant difference in success rate between the groups indicating intracameral voriconazole and oral ketoconazole. It can be implemented as an additional modality of targeted drug delivery. Various treatment variables are also responsible for poor outcome, including a shorter stay of intracameral voriconazole in the anterior chamber, the poor corneal concentration of the drug, non-drainage of hypopyon, and individual clinical response. The injection of a higher dosage of the drug or combination therapy with other drugs may improve the outcomes. A study with a large sample size and study group with drainage of hypopyon would be required to confirm these associations.

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Conflict of interest

The authors declare no conflict of interest which could influence their opinions on the subject and/or the materials presented in the manuscript.

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